Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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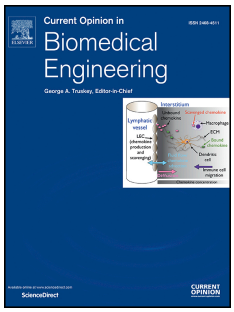

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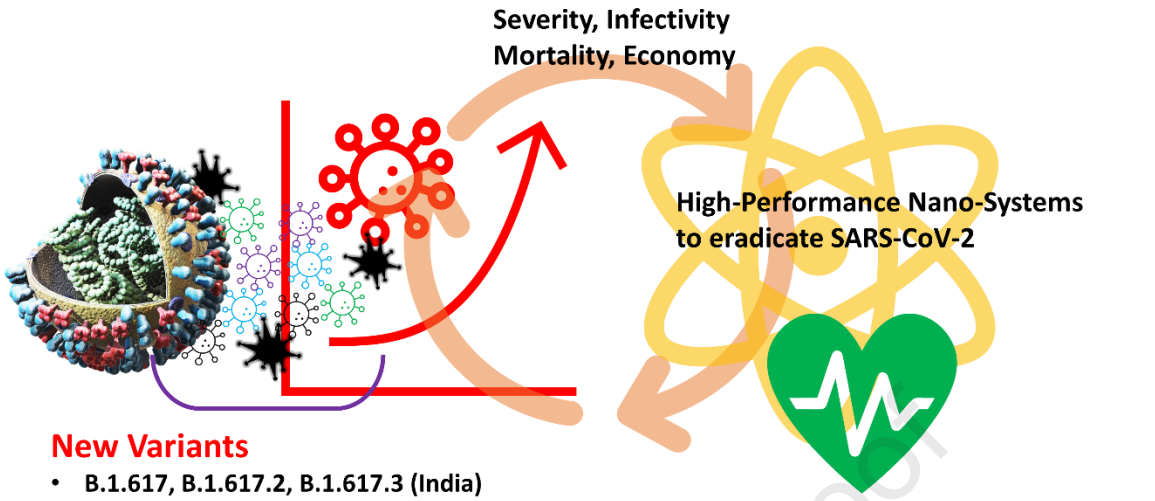

New Variants

- B.1.617, B.1.617.2, B.1.617.3 (India)
- B.1.1.7, B.1.525, B.1.1.318 (U.K)
- B.1.351 (South Africa)
- P.1 (Japan, Brazil)

Precise and Personalized COVID-19 management

Human-to-Human Transmission Mode
A – Droplet
B – Aerosol
C – Air-Dispersed-Aerosol
D – Virus @ Particulate ($PM_{2.5/10.0}$)

Antibacterial and antiviral high-performance nano-systems to mitigate new SARS-CoV-2 variants of concerns

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Abstract: The increased severity of COVID-19 infection due to new SARS-CoV-2 variants have resonated pandemic strategies to re-evaluate effectiveness of pandemic management strategies. This becomes critical due to the shortcomings in the existing global healthcare system in all the developed countries. The designing of high-performance nanosystems (NSs) with tunable performances seems to be the most efficient method to tackle infectious SARS-CoV-2 variants. The opinion projects the versatile functionalized NSs and their innovative potential to mitigate SARS-CoV-2 pathways by sensitization of virus, anti-pathogenicity, photocatalysis, photo-thermal, immune response, and development of ultrasensitive assays for SARS-CoV-2 or associated selective biomarkers identification. In this direction, we propose the fabrication of nano-enabled protective gears, masks, gloves, sheets, filtration units, nano-emulsified disinfectants, paints, and detection systems to facilitate improved quarantine or antiviral spaces. Functional protective gears can even tackle the aerosol distribution of infectious strains transmitted through respiratory fluids and pollutants within droplets, aerosols, air, and particulates.

Keyword: Multi-functional nanosystem, trapping and mitigation of COVID-19, intelligent nano-healthcare, and Effective management of virus.

1. Introduction: Emergence to manage CoV-19 pandemic

The recent pandemic (COVID-19 viral infection pandemic/endemic or both) has been identified to be caused by a new human coronavirus with crown-like spike protein or 'corona' (SARS-CoV-2) [1–4]. The technological advances, active scientific collaborations, and emergency responses by countries were rewarded by the discovery of vaccines with higher efficacy to combat COVID-19 infection. Vaccines developed by Pfizer, Moderna, CoVaxin, Johnson & Johnson and others were deemed to be very effective against the first stage of COVID-19 infection. However, mutations, varied human physiology, and regional changes make it difficult to manage the multiform virus. As of today billions of deaths are ascribed to the SARS-CoV-2 infection, and the number is growing every second even after partial vaccination [5]. All the variants are now characterized as variants of high concerns (VOC):- Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), and Delta (B.1.617.2), whereas, few other are under variants of interest (VOI):- Epsilon: B.1.427/B.1.429, Zeta: P.2, Eta: B.1.525, Theta: P.3 , Iota: B.1.526 , and Kappa: B.1.617.1 [5]. Moreover, new variants have a wider reach and probably can further mutate to affect the global younger population. Although the pandemic situation in many countries like China, the USA, Canada, the UK, New Zealand, and others are relatively better due to proper vaccination drives and public health orders. However, even a small underestimation of the COVID-19 pandemic situation may lead to catastrophe, as observed by a sudden rise in number of cases all over India during the second and third wave, which was similar to the rapidly spread at the first stage in Italy, Brazil, China, and the USA [6–8].

A viral outbreak is not new to human existence, but what makes SARS-CoV-2 a significant threat is its 40-fold higher transmission efficiency than SARS-CoV-1 and a 3.3% higher fatality rate. All statistics highlight the mutation or evolution of infectious diseases over earlier infections, such as the 1967 or 1918 Influenza (0.6%, 2% respectively) pandemic. Moreover, consistent genetic mutations in the viral genome make it difficult to subdue its effect. The coronavirus SARS-CoV-2 infection is not limited to infecting the lungs and causes biological complications, syncytia, and an unpredictable increase in blood clotting chemicals. Different drug formulations are under trial, while some have already been approved for emergency uses against the catastrophic effect of COVID-19 infection. However, limited efficacy, safety, and adverse immune responses have restricted their generalized application of few of those vaccines. The strategy to revive the essential facilities during/ post-pandemic situations involves the healthcare industry imbibing the very essence of nanotechnology. The imbalance in population and rate of vaccine production, vaccine stocks, and other medical facilities, especially in developing or economically challenged countries, has also suggested the requirement of alternate ways to utilize a small quantity of functional material for a larger population without compromising the efficacy [9–12]. Nano-enabled devices/ formulations like nano-structured high-performance materials, development of ultrasensitive diagnostic platforms, improved bio-imaging modalities, advanced point-of-care devices, antiviral therapies, and drug formulations in response to emerging viral diseases abounds literature [3,13]. We hypothesize that the consequences and impact of new SARS-CoV-2 variants could be more efficiently managed using advanced nano-assisted approaches, as illustrated in Figure 1A. Although prevalent for a few decades now, nanotechnology has found new relevance in healthcare in the present scenario when COVID-19 controlling and managing pre/post infection consequences are the main priority of health agencies and experts, as illustrated in Figure 1B. [14–16].

In this direction, this opinion article explores nano-technology based alternate medicinal platforms, mediated through nanomaterials to address or mitigate such viral outbreaks. In this report, our focus is on the potential routes of NSs-assisted strategies such as antibacterial/viral coating and membranes, lipid encapsulated drug formulations of improved efficacy, immune capture assisted sensors amongst others to combat COVID-19 infection, and a way forward to assess the limitations of nanotechnology [17–19].

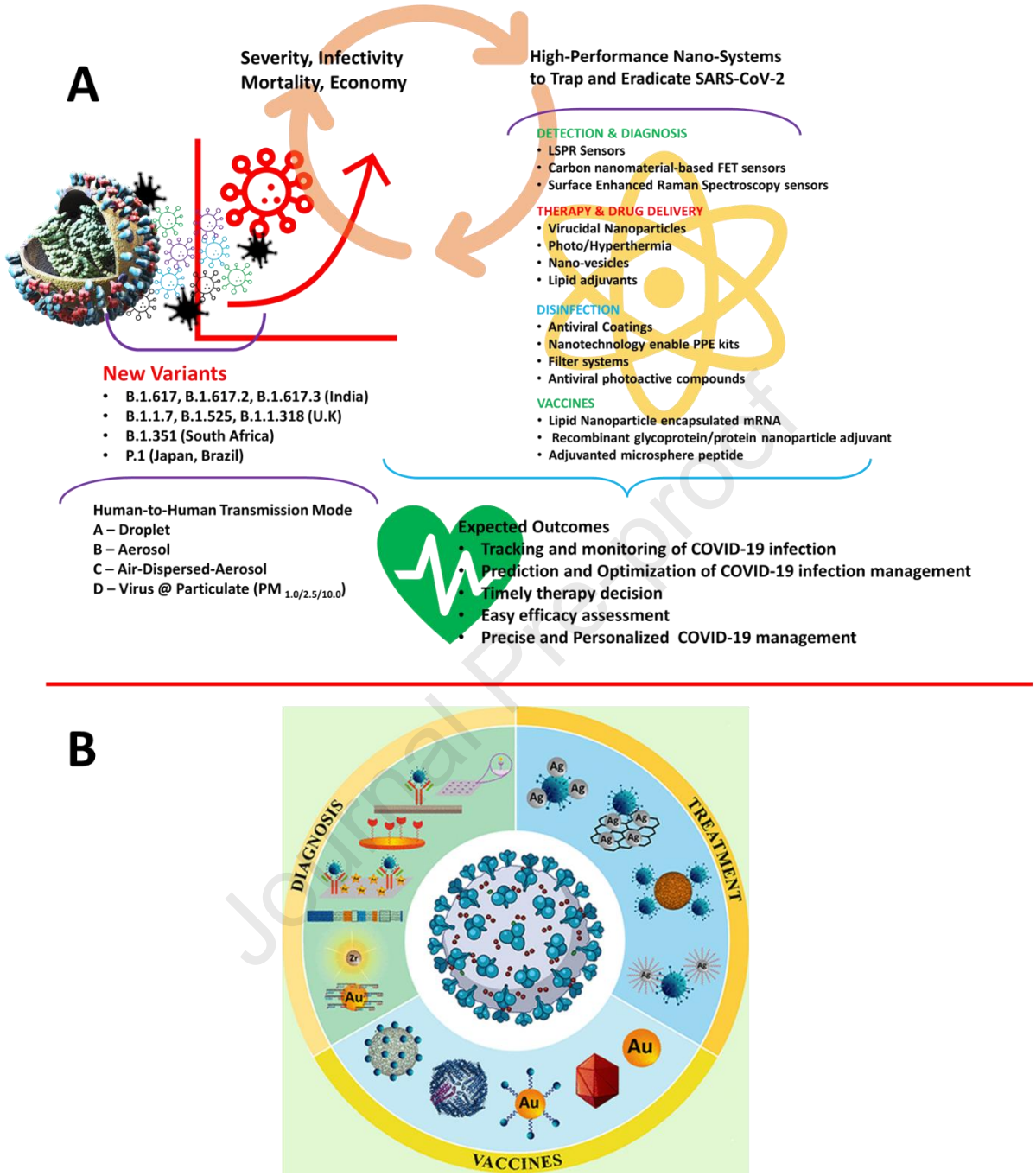

Figure 1. A) Prospective of NSs-supported approaches and strategies to mitigate COVID-19 viral infections caused by new SARS-CoV-2 variants of concerns (A), Illustration of state-of-art nanosytem investigated for diagnorics, treatment and vaccine delivery to manage COVID-19 efficient (B, **Copyright ACS 2021**).

2. NSs-supported COVID-19 pandemic/endemic mitigation

The potential of high-performance NSs with desired functional properties in biomedicine is well documented. However, their clinical application is still under consideration, but their prospects are immense, specifically in antiviral research [20]. Some common advantages of nanomaterials against viral diseases include **i)** tunable physicochemical properties with inherent antiviral/antimicrobial, **ii)** Improved

drug loading efficacy owing to high specific surface areas, **iii)** Increased circulation time in the body, modulating drug circulation time *in-vivo*, **iv)** assists delivery of water-insoluble drugs, and **v)** ultrasensitive detection capabilities based on superior optical/electronic behavior such as Localized Surface Plasmon Resonance (LSPR).

The current antiviral strategies, including neutralizing antibodies, vaccines, and drugs, are driven using the NSs-based nanomedicine approaches (Figure 2A) which facilitates global distribution. For example, the limited efficacy of Dexamethasone to treat hyperactive immune cells is subjugated by intravenous delivery of nanoformulations in SARS-CoV-2 patients. Similarly, the neutralizing antibodies (LY3819252\REGN10933/ REGN10987) and fragments (INOSARS) have been developed for fighting SARS-CoV-2 consisting of nano-scaled Ab fragments, known as nano-bodies. Nano-enabled antiviral vaccines have the most sought out, strongest, and efficient response to a viral outbreak. The efficacy predominately depends on the stability of its delivery vehicle, that are in nano regime [21,22]. For example, the lipid molecules in the mRNA-1273 from Moderna Inc. or the ChAdOx1 nCoV-19 from Oxford University require a non-replicating adenovirus vector, all of these can be considered as NSs. The objective is mostly the implementation of a nano-enabled medical platform to trap the virus, enhance detection, and protection efficiency, thereby, restricting the propagation.

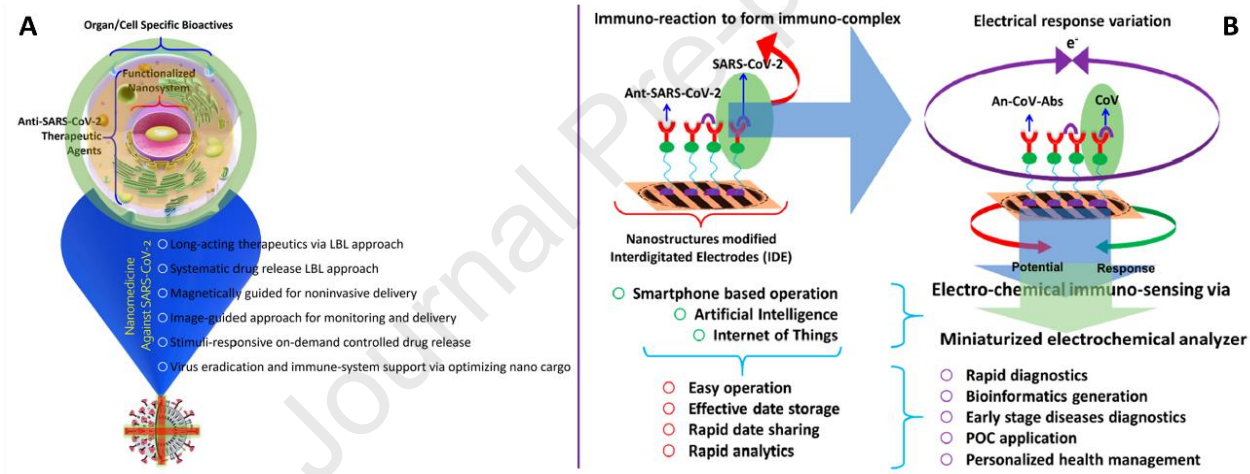

Figure 2. The NSs-assisted high-performance nanomedicine **(A, Copyright Dovepress 2020)** and biosensing approach **(B, Copyright ACS 2020)** to combat COVID-19 infection intelligently in a personalized manner.

Prior to vaccination, rapid detection of the viral strain within or outside the body has been a challenge. NSs-based methodologies have been reported which can overcome this limitation in the detection of viral load concentration. These NSs becomes highly suitable for quick response strategies at airports, hospitals, and quarantine centers due to shorter response time, lower detection limit, bio-functional, tunable, and other enhanced surface phenomena [23]. One such example includes the development of a testing kit by ETH in Switzerland, thereby tapping the multiplexing effect of the nanomaterials [24]. A combination of photo-thermal and LSPR characteristics of the plasmonic nanoparticles allowed true SARS-SARS-CoV-2 detection with promising potential for sensitive clinical diagnosis. The graphene-based FET system could detect SARS-CoV-2 spike in proteins at a concentration as low as femtomole in a clinical transport medium. Furthermore, the two-dimensional gold (Au) nano-islands functionalized with complementary DNA receptors selective for SARS-CoV-2 allowed detection through nucleic acid hybridization, which was

affirmed using thermos-plasmonic heat mapping in picomolar (pM) range [3]. The aspects of the nano-enabled biosensor to manage COVID-19 infection intelligently and in a personalized manner are illustrated in Figure 2B.

3. NSs infused surface coatings, protective sieves & disinfectants

The NSs with highly sensitive multifunctional properties can check the pathogens' genesis, replication, and genetic makeup. Thus, they can be highly effective in containment protocols, drug formulation, rapid testing kits, and mitigation strategies. Nanotechnology addresses most of the present concerns for viral infections. It has also proven to be a successful alternative against existent viral pathogens such as HIV, herpes, and other respiratory viruses [25–27]. The NSs, are distinguished by their high specific surface area, functional values, optical and electrical tunability, efficient charge transfer abilities, inherent photocatalytic and antiviral/microbial properties. They have rightfully drawn researchers' interest around the world to tackle adversities.

They can address various problems against infections through multiplatform approaches, as nano-sensors, nano-assisted assays, delivery agents, and antiviral agents/sterilizers [4,13,23,28,29]. Drugs with poor aqueous solubility but high inhibition abilities can be easily delivered intravenously with controlled concentration and lowered toxicity. Nano drug carriers such as nanoemulsions, polymersomes, nanosomes, lipid-protein based vehicles, etc., have been established for high drug encapsulations, ability to influence the drug pharmacokinetics, and sustained drug release. Moreover, surface binding nanoparticles with specific recognition molecules brings specificity and is also known to boost antiviral properties [18,30]. The encapsulation of drugs within the nanocarriers improved their shelf lives and therapeutic effect during in vivo reactions. These strategies would certainly work well with COVID-19 and cytokine storm or excessive pro-inflammatory cytokines [31,32]. Composite materials such as boric-acid-carbon quantum dot composite can target HCoV-229 E human coronavirus by readily interacting with the viral receptors and the viral S protein. Interference with cellular binding restricts replication [33]. Modified Au-NSs, mimicking heparan sulfate proteoglycan (HSPGs) have inhibited viral attachment, entry, and spread [34]. The siRNA-assisted approach or nanoencapsulation-cum-delivery can contain SARS-CoV-2 spread by targeting pathogenicity caused by S protein and 3`UTR of the virus [30,35]. CRISPR-based systems have also been highlighted as an alternative for SARS-CoV-2 inhibition. Viral degradation and inhibition were brought about using Cas13d RNA endonucleases and targeted RNA synthesis using guide RNA [36]. The siRNA and CRISPR might not directly involve nanoparticles for viral restriction, but they have been identified as nanomachinery working towards virulence address. Other than blocking the viral entry and replication, nanoparticles can also assist in improving the drug efficacy by improving bioavailability.

Viral infection in the atmosphere may affect others and can be responsible for the rapid spread of the disease. Doremalen and Kampf have reported the persistence of SARS-CoV-2 in the air and on various surfaces for days at temperatures above 30 °C [37,38]. Strong disinfectants or chemicals can kill the pathogens but can also make them resistant or cause mutations. At the same time, nanomaterials with high specific surface areas, localized drug release, slow disinfectant release profiles, stimuli responsiveness, and indigenous antimicrobial or self-cleaning properties could be used. They could address major concerns such as deparaffination, volatilization, and degradation associated with the conventional alcohol-based disinfectants [39,40]. The NSs composed of ZnO, Mn, Fe, CuO, CeO_2, graphene oxide, Ti, Ni, Ag, Au, etc., can be spray coated on cloth or maybe infused within the fiber to project the anti-contaminated platform. These NSs promote oxidation reactions on their surfaces with the help of the trapped oxygen moieties, stimuli (light/electrochemical) responsive, and can undergo several charge-discharge cycles. Functionalized nanostructures can adhere to the virus or other germ particles and disinfect the same by inherent variation in the magnetic field (hyperthermia), electric, or optical fields.

NanoTech Surface's, like titanium dioxide-silver nanoparticle-based disinfectant, was recently used to clean the buildings in Milan and was reported to be an effective self-sterilizing formulation limiting microbial buildup [2,41]. The TiO_2-based photocatalytic coatings developed by FN Nano Inc., also have been tested to be an effective antiviral agent due to the ability to damage viral membranes upon light activation **(Fig. 3A,)** [42]. The coating of such viable functional materials over metal surfaces, air-conditioner vents, hospital floor mats, and equipments can enhance the protection mechanism.

Alternatively, fabricating nano-scaled 3D structures with hydrophobic nanomaterials has also been known to prevent droplet accumulation, indulging self-cleaning approach. Nanomaterials can also be used to develop antimicrobial textiles for use in PPE, masks, and sheets. Nano-engineered polymers, quaternary ammonium salts, peptides, metal oxides restrict microbial growth by facilitating microbial membrane dissociation through oxidation. The high surface areas can be easily functionalized with other nanomaterials to restrict viral replication on the nanomaterial surface. The ability to generate reactive oxygen species, photo-thermal and photocatalytic properties presents them as a potential disinfectant with high viability [29]. Similarly, LIGC Applications Ltd. developed reusable masks made out of graphene foam (Guardian G-Volt), which can protect and be sterilized against SARS-CoV-2 [43,44]. Even biopolymers in nano assemblies have antiviral potential, such as nano-cellular sponges fabricated from human epithelial cells (Type-II) functionalized with inherent protein receptors can neutralize infecting ability of SARS-CoV-2 (**Fig. 3B**) [45]. The films or coated surface over the PPE kit can produce optimum inhibition against viruses and other inflammatory diseases.

Even nanomaterial-infused face masks, lab coats, gloves, and instrument surfaces are engineered to include new features such as antimicrobial, hydrophobicity, self-cleaning, and healing properties **(Fig. 3 C & D)** [46–49]. Toxicity is a big concern since the development of these functional materials; however, the adhered nano-entities on the surface of such material would only enhance the beneficial aspects over others. It increases the reusability, faster regeneration via stimuli-responsive mechanisms, and even reduces the cost of the material in the long run. Tuned nanomaterials with high hydrophobic characteristics can act as an effective barrier against aerosol-mediated viral transfer, which happens to be the most probable infection route at the present moment. Compared to regular cotton/ three-layered cloth face masks, combining a billion smaller fragments builds up significant surface tension allowing prevention of droplet absorption simultaneously with antiviral/ bacterial response to the environment. Engineered nano-disinfectants based out of nanostructured water with active agents can significantly reduce viral reduction, including influenza H1N1. The high surface areas allowed a significant reduction in dosage to nanograms indicating high viability [50]. NanoSeptic formulated self-cleaning crystal nanoparticles have also presented environmentally sustainable alternatives with no residual discharge [51]. However, consequential effects on prolonged use, wear-off properties during washing, possible skin irritations, and allergies are tested for nanotechnology-enabled material for broader applications.

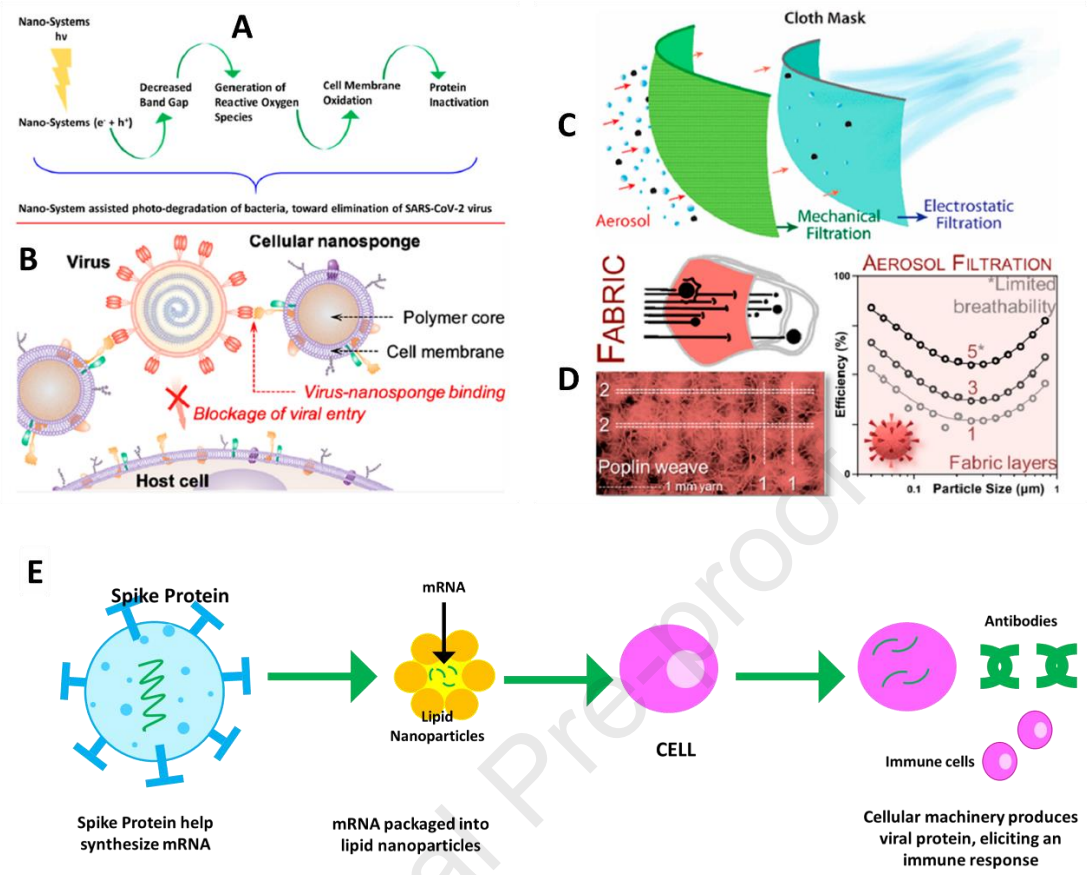

Figure 3. Nano (TiO_2)-assisted approach to eradicate micro-organism on light stimulation **(A)** [52], Antiviral biopolymer coated surface to eradicate virus **(B,** Copyright ACS 2020**)** [45], **C)** cloth-based mask (three-layered, a combination of cotton silk, chiffon, and flannel fabric) to trap SARS-CoV-2 containing aerosol (< 300 nm and efficiency of 85%) for avoiding transmission **(C, Copyright ACS 2020)** [47], Fabric (synthetic/cotton blend, wool, cotton, synthetic, and synthetic blend) dependent performance of a mask to trap aerosol virus useful to avoid infection transmission**(D, Copyright ACS 2020)** [46], **E)** NSs-assisted approach to delivery vaccine inside the cell.

4. Antiviral nano-vaccines and delivery vehicles

High-performance NSs contribute to vaccines by acting as adjuvants or carriers as well as effective barriers. NSs-supported vaccines (i.e., nanomedicine) protect antigens against premature degradation, can cross cell membranes, allow sustained release, enhance stability and encourage targeted immunogen delivery [41]. The BNT162b, one of the probable COVID-19 vaccines, BioNTech and Pfizer, contains lipid-based nano-formulation. As a result, the pre-fusion conformation of S protein and the receptor-binding domain is maintained, allowing for neutralizing immune cells **(Fig. 3E)** [29]. Imperial College, London, and Acuitas Therapeutics, Canada, also jointly developed a self-amplifying RNA–lipid nanoparticle encapsulated with pre-fusion SARS-CoV-2 protein to produce a second-generation vaccine variant [30]. Encapsulation of genetic matter in lipid nanoparticles allows protection from enzymatic degradation while increasing cellular uptake. Moderna (patent WO2017070626 and WO2018115527), the very first mRNA-based nano-vaccine, encapsulates mRNA mix into lipid nanoparticles, such that it could encode MERS-CoV S protein in vivo in mice to elicit an immune response. Novavax Inc. developed a recombinant SARS-CoV-2 vaccine with mutations at different sites in S protein to protect it from cleavage and to maintain the pre-

virulence stage configuration. The NVX-CoV2373 is presently in phase 1/2 of the clinical trials. In addition to the commonly targeted S protein, a mix of proteins, such as nucleoproteins and non-structural antigens, also make good candidates for vaccine production [41,53]. The Epivax works on this concept of a "cocktail" vaccine that aims to provide partial protection against the SARS-CoV-2 while the specific vaccines are underway. In another such effort, Matrix-M adjuvant improves immunological response by stimulating the antigen-presenting cells at the injection site. Different immuno-modulatory therapies are prevalent to induce passive immunity, neutralizing antibodies, or convalescent plasma to mankind to achieve mass immunization against the SARS-CoV-2 [29,30,41]. However, the critical needs of an effective vaccine, immune parameters FET governing the hosts, precluding any adverse reactions, still need careful observations and enough clinical trials to achieve sustained antiviral efficacy from a nano vaccine.

5. Challenges, viewpoint, & future aspects

We anticipate more FDA approvals to antiviral/bacterial NSs for managing COVID-19 or other infections via trapping and neutralizing, thus effectively eradicating existing VOCs. As the existing NSs are smart, affordable, acceptable, and have also shown the potential to be (i) protective agent by surface coverings, membranes, masks, gloves, (ii) drug delivery by increasing the retention of drug and targeted delivery (i.e., nanomedicine towards personalized treatment), and (iii) biosensor for prevention and early-stage diagnostics suitable for POC application. Overall, this approach is towards intelligent COVID-19 management in a personalized manner. However, such NSs are limited, and scaling up must be a future direction due to considering the significance of demonstrated application. Advanced techniques including microfluidics, cold plasma, and supercritical formulation methodologies could also be explored for such formulations. Further, engineered lipid-based nanoformulation would be largely exploited in the recent future in biomedicines, anti-viral/bacterial, and coating technologies with possible biomodifications using proteins or other biodegradable plant based materials.

In this unprecedented scenario of the COVID-19 pandemic, avoiding SARS-CoV-2 transmission is a top priority, as new VOC and VOI have emerged with rapid transmission and severity. Besides that, the airborne and particulate-assisted transmission of SARS-CoV-2 is detrimental. This raised the concerns and projected new approaches such as NSs assisted anti-viral/bacterial devices for protection against infection. We believe that using these NSs in filter technology, air-conditioners, exhaust, masks, hydrophobic coverings, sheets, clothes, and other forms of disinfectant would be revolutionary. This approach may not seem fully functional due to limited resources and lacking execution, but the potential of NSs in improving these strategies cannot be ruled out. Table 1 highlight few of the many NSs which have been proved or similar platforms would be used to be highly efficient against pandemic situations. However, some common breakers include the high cost of specific biomarkers, storage infrastructures, and skilled resources to improve medicine from lab to home.

Table 1. Few of the many NSs with multifunctional abilities.

S.No.	Platform	Inhibition activity/ functionality	Ref.
1.	Plasmonic gold nanoparticles	Naked-Eye Detection of SARS-CoV-2 Limit of detection as 0.18 ng/μL	[28]
2.	Functionalized gold nanoparticles	Femto molar detection with ultranarrow lineshapes in the terahertz (THz) frequencies	[13]
3.	Silver nanocluster/silica composite coatings	Virucidal effect on SARS-CoV-2, flexible ceramic with practical applications	[16]

4.	Lipid nanoparticles	Immunization response against pseudotyped and wild-type SARS-CoV-2 virus	[30]
5.	Carbon quantum dots	Inactivation of CoV strain through inhibition of protein S-receptor interaction	[33]
6.	Electrospun nanofibers, ZnO Nanorods and Ag Nanoparticles	Antibacterial, antiviral, self-cleaning, and sensing mats for clothing aplications	[39]
7.	Nanostructure substrate (cellular nanosponges)	Trapping and nutralization of SARS-CoV-2	[45]

The spread of nano-biotechnology tools and techniques improving our lives is undoubtedly fascinating. However, efficient drug packaging in nano-vesicles/pores or simply on their surfaces and prolonged retention in the tissues are still to be perfected for large-scale production/ population. In this regard, protein-based nanoemulsions can simultaneously neutralize SARS-CoV-2 and deliver essential drug molecules. Just like cancer, viral infection showing severe heterogeneity due to a certain degree of mutation over alternating physiological parameters, emphasizes the need for personalized medicine. Additionally, frequently mutating strains, for example, the double mutant B1.617 is modified at Ab binding sites, ticking off effective association against designed aptamers failing the entire sensing platform is a challenge. Therefore, re-evaluating the sensing, treatment, and neutralizing capability to overcome the severity of new SARS-CoV-2 variants of concerns is needed to combat COVID-19 infection globally.

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CONFLICT OF INTEREST: The authors declare no conflict of interest.

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Highlights

- Nano-systems for efficient sensing, treatment, and inhibitors are required to manage COVID-19 pandemic.
- Development of anti-viral and anti-bacterial nano-systems to trap and neutralize SARS-CoV-2.
- These systems can be efficient barriers to manage human-to-human transmission of SARS-CoV-2.
- Airborne and particulate base transmissions are manageable using nanotech-systems.
- Delivery of COVID-19 vaccines to the targeted sites using smart nano-vehicles as transporters.

Declaration of Competing Interest

There are no conflicts of interest declared by the authors.